We claim:

1. An isolated antibody, or an antigen-binding portion thereof, that dissociates from human erythropoietin receptor (EpoR) with a K_{off} rate constant of greater than about 1.3 $x10^{-3}$ s^{-1} and that activates an endogenous activity of said human EpoR in a mammal.

2. The antibody or antigen-binding portion thereof of claim 1 wherein said K_{off} rate constant is about 1.4 $x10^{-3}$ s^{-1} or greater.

3. The antibody or antigen-binding portion thereof of claim 1 wherein said K_{off} rate constant is about 1.9 $x10^{-3}$ s^{-1}.

4. The antibody or antigen-binding portion of claim 1 wherein said K_{off} rate constant is about 4.8 $x10^{-3}$ s^{-1}.

5. The antibody or antigen-binding portion of claim 1 wherein said K_{off} rate constant is determined by surface plasmon resonance.

6. The antibody or antigen-binding portion thereof of claim 1 wherein said antibody is a monoclonal antibody.

7. The antibody or antigen-binding portion thereof of claim 6 wherein said antibody is an IgG2 isotype.

8. The antibody or antigen-binding portion thereof of claim 1 that binds to human EpoR with a K_d of about 7 nM or greater.

9. The antibody or antigen-binding portion thereof of claim 8 wherein said K_d is about 8.5 nM or greater.

10. The antibody or antigen-binding portion thereof of claim 8 wherein said K_d is about 20 nM.

11. The antibody or antigen-binding portion thereof of claim 8 wherein said K_d is about 32 nM.

12. The antibody or antigen-binding portion thereof of claim 8 wherein said K_d is about 7-32 nM inclusive.

13. The antibody or antigen-binding portion thereof of claim 1 which is a human antibody.

14. An antibody or antigen-binding portion thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal comprising a heavy chain variable region (HCVR) comprising an amino acid sequence of Formula I:

Y-I-X_1-X_2-X_3-G-S-T-N-Y-N-P-S-L-K-S (SEQ ID NO:18)

wherein:

X_1 is independently selected from the group consisting of tyrosine (Y), glycine (G) and alanine (A);

X_2 is independently selected from the group consisting of tyrosine (Y), glycine (G), alanine (A), glutamine (E) and aspartic acid (D); and

X_3 is independently selected from the group consisting of serine (S), glycine (G), glutamine (E) and threonine (T)

with the proviso that X1-X2-X3 is other than Y-Y-S.

15. The antibody or antigen-binding portion thereof of claim 14 wherein X_1 is G and X_2 and X_3 are as defined therein.

16. The antibody or antigen-binding portion thereof of claim 14 wherein X_2 is G and X_1 and X_3 are as defined therein.

17. The antibody or antigen-binding portion thereof of claim 14 wherein X_3 is E and X_1 and X_2 are as defined therein.

18. The antibody or antigen-binding portion thereof of claim 14 wherein X_1 is G, X_2 is G and X_3 is as defined therein.

19. The antibody or antigen-binding portion thereof of claim 14 wherein X_1 is as defined therein, X_2 is G and X_3 is E.

20. The antibody or antigen-binding portion thereof of claim 14 wherein X_1 is G, X_2 is G and X_3 is E.

21. The antibody or antigen-binding portion thereof of claim 14 wherein X_1 is A, X_2 is G and X_3 is T.

22. An antibody or antigen-binding portion thereof comprising an amino acid sequence selected from the group consisting of

(a) YIGGEGSTNYNPSLKS (SEQ ID NO:19);

(b) YIAGTGSTNYNPSLKS (SEQ ID NO:20);

(c) YIGYSGSTNYNPSLKS (SEQ ID NO:21);

(d) YIYGSGSTNYNPSLKS (SEQ ID NO:22);

(e) YIYYEGSTNYNPSLKS (SEQ ID NO:23);

(f) YIGGSGSTNYNPSLKS (SEQ ID NO:24);

(g) YIYGEGSTNYNPSLKS (SEQ ID NO:25); and

(h) YIGYEGSTNYNPSLKS (SEQ ID NO:26).

23. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 1.

24. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering

to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 2.

25. A method of modulating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 3.

26. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 4.

27. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 6.

28. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 7.

29. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 8.

30. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 10.

31. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 11.

32. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim13.

33. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim14.

34. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 15, 16, 17, 18, 19, 20 or claim 21.

35. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 22.

36. A method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of the antibody or antigen-binding portion thereof of claim 1.

37. A method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of the antibody or antigen-binding portion thereof of claim 13.

38. A method of treating a mammal suffering anemia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of the antibody or antigen-binding portion thereof of claim 1.

39. A method of treating a mammal suffering anemia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of the antibody or antigen-binding portion thereof of claim 13.

40. A pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 1 and a pharmaceutically acceptable excipient.

41. A pharmaceutical composition comprising a therapeutically effective amount of an antibody or antigen-binding portion thereof of claim 13 and a pharmaceutically acceptable excipient.

42. An isolated or purified polynucleotide sequence which encodes a polypeptide comprising an amino acid sequence of Formula I:

Y-I-X_1-X_2-X_3-G-S-T-N-Y-N-P-S-L-K-S (SEQ ID NO:18)

wherein:

X_1 is independently selected from the group consisting of tyrosine (Y), glycine (G) and alanine (A);

X_2 is independently selected from the group consisting of tyrosine (Y), glycine (G), alanine (A), glutamine (E) and aspartic acid (D); and

X_3 is independently selected from the group consisting of serine (S), glycine (G), glutamine (E) and threonine (T)

with the proviso that X1-X2-X3 is other than Y-Y-S.

43. The polynucleotide of claim 42 wherein X_1 is G and X_2 and X_3 are as defined therein.

44. The polynucleotide of claim 42 wherein X_2 is G and X_1 and X_3 are as defined therein.

45. The polynucleotide of claim 42 wherein X_3 is E and X_1 and X_2 are as defined therein.

46. The polynucleotide of claim 42 wherein X_1 is G, X_2 is G and X_3 is as defined therein.

47. The polynucleotide of claim 42 wherein X_1 is as defined therein, X_2 is G and X_3 is E.

48. The polynucleotide of claim 42 wherein X_1 is G, X_2 is G and X_3 is E.

49. The polynucleotide of claim 42 wherein X_1 is A, X_2 is G and X_3 is T.

50. The polynucleotide of claim 42 selected from the group consisting of

(a) YIGGEGSTNYNPSLKS (SEQ ID NO:19);
(b) YIAGTGSTNYNPSLKS (SEQ ID NO:20);
(c) YIGYSGSTNYNPSLKS (SEQ ID NO:21);
(d) YIYGSGSTNYNPSLKS (SEQ ID NO:22);
(e) YIYYEGSTNYNPSLKS (SEQ ID NO:23);
(f) YIGGSGSTNYNPSLKS (SEQ ID NO:24);
(g) YIYGEGSTNYNPSLKS (SEQ ID NO:25); and
(h) YIGYEGSTNYNPSLKS (SEQ ID NO:26).

51. A recombinant expression vector comprising the polynucleotide of claim 42.

52. A host cell comprising the recombinant expression vector of claim 51.

53. The host cell of claim 52 which is a eucaryotic cell.

54. The host cell of claim 52 which is a mammalian cell.

55. The host cell of claim 52 which is yeast cell.

56. The host cell of claim 52 which is a bacterial cell.

57. The host cell of claim 52 which is a CHO cell.

58. The host cell of claim 52 which is a COS cell.

59. The host cell of claim 52 which is an HEK-293 cell.

60. A polypeptide sequence encoded by said polynucleotide sequence of claim 42.

61. A polypeptide molecule comprising a first polypeptide sequence, a second polypeptide sequence, and a linking sequence, wherein:

said first polypeptide sequence is capable of binding a ligand;

said second polypeptide sequence is capable of binding a ligand;

said linking sequence connects said first polypeptide sequence and said second polypeptide sequence to form a single polypeptide chain; and

wherein said linking sequence comprises one or more amino acid sequences selected from the group consisting of, Gly-Phe-Lys-Asp-Ala-Leu-Lys-Gln-Pro-Met-Pro-Tyr-Ala-Thr-Ser (SEQ ID NO:37), Gly-His-Glu-Ala-Ala-Ala-

Val-Met-Gln-Val-Gln-Tyr-Pro-Ala-Ser (SEQ ID NO:4), Gly-Pro-Ala-Lys-Glu-Leu-Thr-Pro-Leu-Lys-Glu-Ala-Lys-Val-Ser (SEQ ID NO:3), and Gly-Glu-Asn-Lys-Val-Glu-Tyr-Ala-Pro-Ala-Leu-Met-Ala-Leu-Ser (SEQ ID NO:2).